Accompanying Documents

1. Copy of the currently pending claims (Appendix A).
2. Copy of "Basic & Clinical Immunology, 6th Edition" (1987) Stites, Stobo, & Wells editors, Appleton & Lange, Los Altos, CA, Figure 17-36.

REMARKS

Introductory Comments

Claims 20-23 and 44-79 are pending. The Examiner has rejected all pending claims.

The Examiner has rejected claims 20, 44 and 56, and the claims that depend on them, under 35 U.S.C. §112, second paragraph, for allegedly being indefinite.

The Examiner has rejected claims 20-23 and 44-79 under 35 U.S.C. §112, first paragraph, alleging that the specification does not reasonably provide enablement for making the specific antibodies.

The Examiner has rejected claims 20-23 and 44-79 under 35 U.S.C. §112, first paragraph, alleging that the specification does not reasonably provide enablement for making the antibody specific for the antigen.

The Examiner has rejected claims 20-23 and 44-79 under 35 U.S.C. §112, first paragraph, alleging that the specification lacked the expected results of the claimed antibodies and examples that show the specificity of the claimed antibody.

These rejections are traversed and believed to be overcome for reasons discussed below.

Addressing the Examiner's Rejections

1. Rejection under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claims 20, 44 and 56, and the claims that depend on them, under 35 U.S.C. §112, second paragraph, for allegedly being indefinite. The Examiner notes that claims 20, 44, and 56 contain the term "specific" and states that it is a relative term which renders the claims indefinite.

Applicants traverse the rejection. Under 35 U.S.C. §112, second paragraph, absolute specificity and precision are not required in the claims. Claims need only reasonably apprize a person having ordinary skill in the art as to their scope. *Hybritech Inc., v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, Fed. Cir. 1986. A claim which is clear to one ordinarily skilled in the art when read in light of the specification, does not fail for indefiniteness. *Allan Archery, Inc. v. Browning Manufacturing Co.*, 819 F.2d 1087, 2 USPQ2d 1490 (Fed. Cir. 1987).

MPEP §2173.05(b) discusses the use of relative terminology in the claims. According to this section of the MPEP, the use of relative terms does not automatically render a claim indefinite. Instead, "[a]cceptability of the claim language depends on whether one of ordinary skill in the art would understand what is claimed, in light of the specification." Thus, the Examiner's broad assertion that the use of relative terminology makes the claims indefinite is incorrect. To the contrary, the use of relative terminology in the claims is acceptable practice, and, as discussed in the case law and in the MPEP, its use should be determined on a case by case basis.

In the present case, one of skill in the art would certainly understand that the relative term "specific" refers to the ability of the antibody to discriminate between different antigens. The antibody of the invention is specific for a glycoprotein expressed from the E1 region of HCV, a glycoprotein expressed from the E2 region of HCV or aggregates thereof, where the glycoprotein has mannose-terminated glycosylation, and where less than about 10% of the total N-linked carbohydrate on said HCV glycoprotein

is sialic acid. One of skill in the art of antibodies would understand that the antibody has greater affinity for the above glycoprotein than for other types of glycoproteins and is therefore specific. The use of the term is not indefinite. The Examiner is respectfully requested to withdraw this rejection.

2. Rejection of Claims 1 and 15 under 35 U.S.C. §112, First Paragraph

The Examiner has rejected claims 20-23 and 44-79 under 35 U.S.C. §112, first paragraph, alleging that the specification does not reasonably provide enablement for making the specific antibodies. The Examiner acknowledges that the specification is enabling for antigen production, but states that the specification does not teach the specific antibodies and there "is no indication of how specific the binding is for the stated HCV glycoprotein or how it differs from antibodies produced from other antigens." Claims 20-23 and 44-79 were additionally rejected under 35 U.S.C. §112, first paragraph, the Examiner alleging that the specification does not reasonably provide enablement for making the antibody specific for the antigen. The Examiner stated that the specification did not provide guidance on how the claimed antibody would be "specific" or react differently than one that is made from an antigen prepared in another way.

The applicants traverse the rejection. The test for enablement is "whether one skilled in the art could make or use the claimed invention from the disclosure in the patent coupled with information known in the art without undue experimentation." United States v Telectronics, Inc. 8 USPQ2d 1217 (Fed. Cir. 1988); In re Wands, 8 USPQ2d 1400 (Fed Cir. 1988). Thus, in order to satisfy Section 112 regarding enablement, the specification need only set forth such information as is sufficient to allow one of ordinary skill in the art to make and use the invention. The burden is on the Office to explain its reasons for the rejection and support the rejection with (i) acceptable evidence, or (ii) reasoning which contradicts the applicants' claim: the reasoning must be supported by current literature as a whole and the Office must prove the disclosure requires undue experimentation. *In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367,

369-70 (CCPA 1971). The Office has failed to provide adequate evidence to support the present rejection. Without such evidence, a rejection under 35 U.S.C. §112, first paragraph for lack of enablement cannot be sustained.

The applicants describe the expression of the asialoglycoproteins of HCV of the claims at page 9, line 24, to page 11, line 20, and in Example 1. The purification of the recombinantly produced asialoglycoproteins is described at page 11, line 21 to page 12, line 25, while Examples 3 and 4 provide detailed steps for purification of the asialoglycoproteins using lectin and further chromatographic purification. The applicants then provide a detailed description for preparing immunogenic compositions using the isolated and purified asialoglycoproteins at page 14, line 24, to page 15, line 28. The applicants have thus enabled the production of the antigen for production of the antibodies specific for the antigen.

As discussed above, the term "specific" refers to the ability of the antibody of the invention to discriminate between a glycoprotein expressed from the E1 region of HCV, a glycoprotein expressed from the E2 region of HCV or aggregates thereof, where the glycoprotein has mannose-terminated glycosylation, and where less than about 10% of the total N-linked carbohydrate on said HCV glycoprotein is sialic acid and other antigens. This discrimination is relative rather than absolute as antibodies may cross-react with a partially related antigen that may have a similar or identical determinant. However, affinity for a partially related antigen would likely be less.

The equations for calculating the binding constant of an antibody for an antigen is well known in the art, and is usually determined using the equation $K = [AbH] / ([Ab][H])$, where [Ab] is the concentration of free antibody combining sites and [H] is the concentration of free hapten. Thus, one of skill in the art could obtain the affinity or strength of binding of the antibody to different antigens, and compare the values to determine specificity, and the degree of cross-reactivity.

Alternatively, there are many well known analytical methods for obtaining specificity. One method, described in "Basic & Clinical Immunology, 6th Edition" (1987)

Stites, Stobo, and Wells editors, Appleton & Lange, Los Altos, CA, pp 268-274, describes the use of immunofluorescence to determine specificity. Figure 17-36 from the text is attached as Appendix B. As is apparent from the figure, quantitative assays, using either direct or indirect immunofluorescence staining techniques to detect specific antibodies were well known at the time of the invention.

The applicants provide detailed instructions for isolating the antigens and for preparing immunogenic compositions using the isolated and purified asialoglycoproteins. From the discussion above, it is apparent that one of skill in the art would know how to determine the specificity of the antibodies produced to the recited antigens by the practice of the applicants' methods. The applicants need not provide information that was already well known in the art. The invention is thus enabled, and the Examiner is respectfully requested to withdraw the rejection.

The Examiner has rejected claims 20-23 and 44-79 under 35 U.S.C. §112, first paragraph, asserting that the specification fails to provide an adequate written description of the invention.

The applicants traverse the rejection. In order to comply with the written description requirement, an applicant's specification must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, i.e., whatever is now claimed. *Vas Cath Inc. v. Mahurkar,* 19 USPQ 1111, 1117 (Fed. Cir. 1991) (cited in MPEP § 2163 and in the Examiner Guidelines on Written Description Requirement). The Examiner has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *In re Wertheim,* 191 USPQ 90 (CCPA 1976) (cited in MPEP § 2163.04 in the Examiner Guidelines on Written Description Requirement). Moreover, it is axiomatic that a patent specification "need not teach, and preferably omits, what is well known in the art." See, *Spectra-Physics, Inc. v. Coherent, Inc.*, 3 USPQ2d 1737, 1743 (Fed. Cir. 1987); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986). Thus, determining whether the written

description requirement is satisfied mandates reading the disclosure in light of the knowledge possessed by those skilled in the art. *In re Alton,* 37 USPQ2d 1578 (Fed. Cir. 1996). Applying these tenets, applicants submit that the Office has failed to carry its burden and that the present claims indeed comply with the written description requirement of 35 U.S.C. §112, first paragraph.

The Office has failed to supply any "evidence or reasons why persons skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims," *In re Wertheim,* 191 USPQ 90 (CCPA 1976). In fact, a review of the application as a whole, coupled with the knowledge in the art at the time of filing, evidences that the application is more than sufficient to convey with reasonable clarity to those skilled in the art that, as of the filing date sought, they were in possession of antibody specific for a hepatitis C virus glycoprotein having mannose-terminated glycosylation.

For example, claim 20 in the application as filed recites:

> 20. An assay kit for detecting the presence of hepatitis C virus (HCV) asialoglycoproteins, said kit comprising:
> a solid support;
> a mannose-binding proteins; and
> **an antibody specific for said HCV asialoglycoprotein**;
> wherein one of said antibody and said mannose-binding protein is bound to said solid support.

(Emphasis added). Based on this claim, it is clear that applicants contemplated antibodies specific for HCV asialoglycoproteins as claimed. Additionally, case law recognizes that original claims constitute their own description. See, e.g., *Massachusetts Institute of Technology v. AB Fortia*, 227 USPQ 428 (Fed. Cir. 1985). Thus, the Examiner has no basis for asserting that the specification fails to provide an adequate written description of the claimed invention.

In view of the above arguments, the applicants submit that claims 20-23 and 44-79 comply with the written description requirement of 35 U.S.C. §112, first

paragraph. The rejection of claims 20-23 and 44-79 under 35 U.S.C §112, first paragraph, for failing to provide an adequate written description of the invention is inappropriate and should be withdrawn.

CONCLUSION

Applicants respectfully submit that the claims comply with the requirements of 35 U.S.C. §112. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

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APPENDIX A

Clean Copy of Claims Pending

20. (Amended) An assay kit for detecting the presence of a hepatitis C virus (HCV) glycoprotein having mannose-terminated glycosylation, wherein less than about 10% of the total N-linked carbohydrate on said HCV glycoprotein is sialic acid, wherein said HCV glycoprotein is selected from the group consisting of a glycoprotein expressed from the E1 region of HCV, a glycoprotein expressed from the E2 region of HCV, and aggregates thereof, said kit comprising:

a solid support;

a mannose-binding protein; and an isolated antibody specific for said HCV glycoprotein;

wherein one of said antibody and said mannose binding protein is bound to said solid support.

21. The assay kit of claim 20, wherein said mannose-binding protein is GNA.

22. The assay kit of claim 20, wherein said antibody is bound to said support and said mannose-binding protein is bound to a detectable label.

23. The assay kit of claim 20, wherein said mannose-binding protein is bound to said support and said antibody is bound to a detectable label.

44. An isolated antibody specific for a hepatitis C virus (HCV) glycoprotein having mannose-terminated glycosylation, wherein less than about 10% of the total N-linked carbohydrate on said HCV glycoprotein is sialic acid, wherein said HCV glycoprotein is selected from the group consisting of a glycoprotein expressed from the

E1 region of HCV, a glycoprotein expressed from the E2 region of HCV, and aggregates thereof.

45. The antibody of claim 44, wherein said HCV glycoprotein is a glycoprotein expressed from the E1 region of HCV.

46. The antibody of claim 44, wherein said HCV glycoprotein is a glycoprotein expressed from the E2 region of HCV.

47. The antibody of claim 44, wherein said HCV glycoprotein is an aggregate of a glycoprotein expressed from the E1 region of HCV and a glycoprotein expressed from the E2 region of HCV.

48. The antibody of claim 44, wherein said HCV glycoprotein is an aggregate of glycoproteins expressed from the E1 region of HCV.

49. The antibody of claim 44, wherein said HCV glycoprotein is an aggregate of glycoproteins expressed from the E2 region of HCV.

50. The antibody of claim 44, wherein the antibody is a polyclonal antibody.

51. The antibody of claim 45, wherein the antibody is a polyclonal antibody.

52. The antibody of claim 46, wherein the antibody is a polyclonal antibody.

53. The antibody of claim 47, wherein the antibody is a polyclonal antibody.

54. The antibody of claim 48, wherein the antibody is a polyclonal antibody.

55. The antibody of claim 49, wherein the antibody is a polyclonal antibody.

56. An isolated antibody specific for a hepatitis C virus (HCV) glycoprotein having mannose-terminated glycosylation, wherein less than about 10% of the total N-linked carbohydrate on said HCV glycoprotein is sialic acid, wherein said HCV glycoprotein is selected from the group consisting of a glycoprotein expressed from the E1 region of HCV, a glycoprotein expressed from the E2 region of HCV, and aggregates thereof, and further wherein said HCV glycoprotein is produced by the method comprising the steps of:

growing a host cell transformed with a structural gene encoding an HCV glycoprotein expressed from the E1 region of HCV or the E2 region of HCV in a suitable culture medium;

causing expression of said structural gene, under conditions inhibiting sialylation; and

isolating said HCV glycoprotein from said cell culture by contacting said HCV glycoprotein with a mannose-binding protein specific for mannose-terminated glycoproteins, and isolating the protein that binds to said mannose-binding protein.

57. The antibody of claim 56, wherein said HCV glycoprotein is a glycoprotein expressed from the E1 region of HCV.

58. The antibody of claim 56, wherein said HCV glycoprotein is a glycoprotein expressed from the E2 region of HCV.

59. The antibody of claim 56, wherein said HCV glycoprotein is an aggregate of a glycoprotein expressed from the E1 region of HCV and a glycoprotein expressed from the E2 region of HCV.

60. The antibody of claim 56, wherein said HCV glycoprotein is an aggregate of glycoproteins expressed from the E1 region of HCV.

61. The antibody of claim 56, wherein said HCV glycoprotein is an aggregate of glycoproteins expressed from the E2 region of HCV.

62. The antibody of claim 56, wherein the antibody is a polyclonal antibody.

63. The antibody of claim 57, wherein the antibody is a polyclonal antibody.

64. The antibody of claim 58, wherein the antibody is a polyclonal antibody.

65. The antibody of claim 59, wherein the antibody is a polyclonal antibody.

66. The antibody of claim 60, wherein the antibody is a polyclonal antibody.

67. The antibody of claim 61, wherein the antibody is a polyclonal antibody.

68. The antibody of claim 56, wherein the structural gene is linked to a sequence encoding a secretion leader that directs the glycoprotein to the endoplasmic reticulum and said conditions inhibiting sialylation comprise inhibiting transport of glycoproteins from the endoplasmic reticulum to the golgi.

69. The assay kit of claim 20, wherein said HCV glycoprotein is a glycoprotein expressed from the E1 region of HCV.

70. The assay kit of claim 20, wherein said HCV glycoprotein is a glycoprotein expressed from the E2 region of HCV.

71. The assay kit of claim 20, wherein said HCV glycoprotein is an aggregate of a glycoprotein expressed from the E1 region of HCV and a glycoprotein expressed from the E2 region of HCV.

72. The assay kit of claim 20, wherein said HCV glycoprotein is an aggregate of glycoproteins expressed from the E1 region of HCV.

73. The assay kit of claim 20, wherein said HCV glycoprotein is an aggregate of glycoproteins expressed from the E2 region of HCV.

74. The assay kit of claim 20, wherein the antibody is a polyclonal antibody.

75. The assay kit of claim 69, wherein the antibody is a polyclonal antibody.

76. The assay kit of claim 70, wherein the antibody is a polyclonal antibody.

77. The assay kit of claim 71, wherein the antibody is a polyclonal antibody.

78. The assay kit of claim 72, wherein the antibody is a polyclonal antibody.

79. The assay kit of claim 73, wherein the antibody is a polyclonal antibody.

APPENDIX B

Figure 17-36 from "Basic & Clinical Immunology, 6th Edition" (1987) Stites, Stobo, and Wells editors, Appleton & Lange, Los Altos, CA.

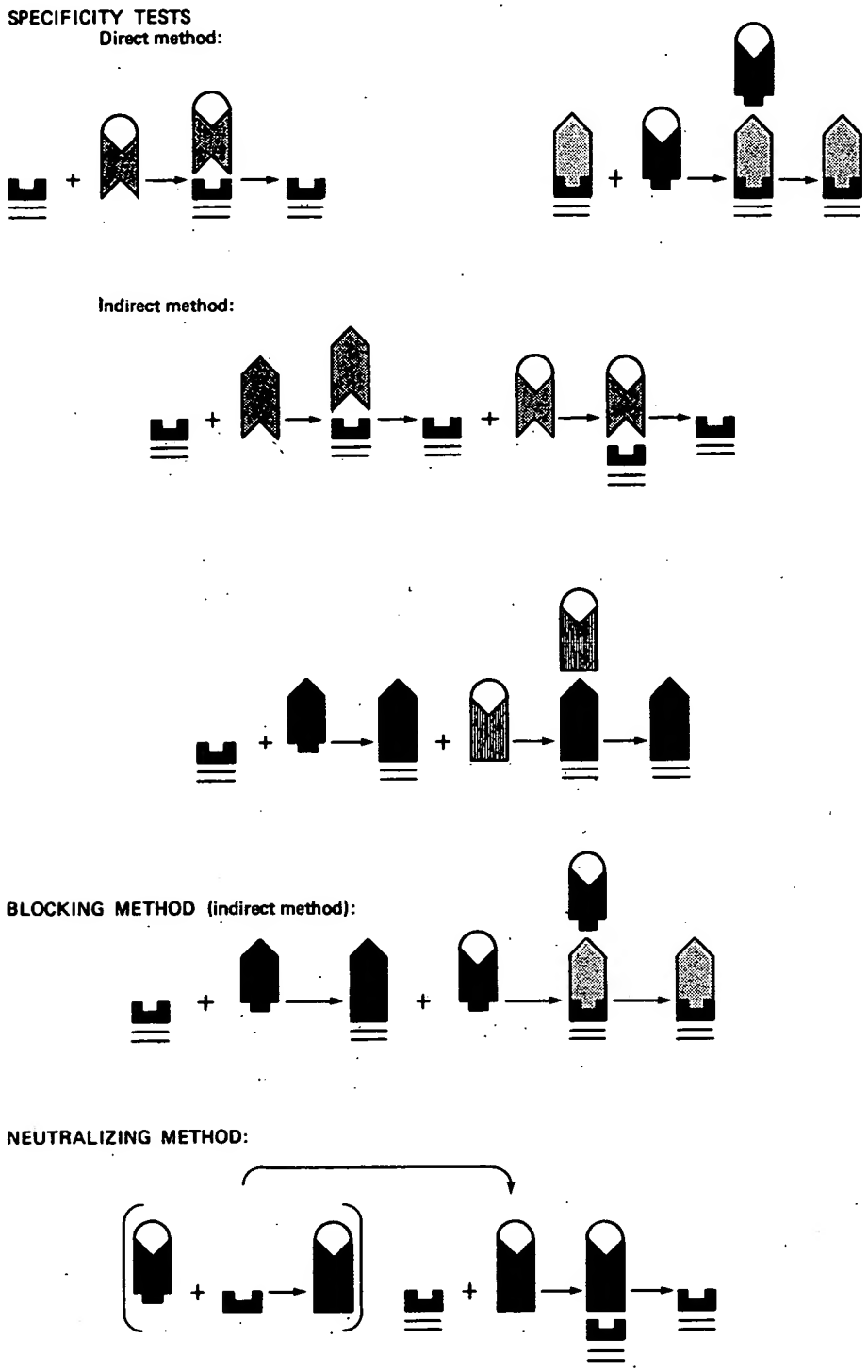

Figure 17–36. Specificity tests. **Direct method.** *(Left):* Substrate antigen fails to react with fluorescent antiglobulin reagent. No fluorescence results. *(Right):* Immune complex-substrate fails to react with fluorescent antibody directed against unrelated antigen. No fluorescence results. **Indirect method.** *(Top):* Unlabeled specific antiglobulin is replaced by unrelated antibody. In second step, fluorescent antiglobulin cannot react directly with antigen in substrate that has not bound specific antiglobulin. No fluorescence results. *(Bottom):* First step performed by reacting specific antibody with substrate antigen. In second stage, the specific conjugate is replaced by unrelated fluorescent heterologous antibody. No fluorescence results. **Blocking method.** Substrate antigen is incubated with unlabeled specific antibody prior to addition of specific fluorescent antibody. Decreased fluorescence results. **Neutralizing method.** Substrate antigen is incubated with specific fluorescent antibody after it is absorbed with specific antigen in substrate. No fluorescence results.